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COMPARISON OF ADEQUACY OF ANALGESIA BETWEEN THORACIC EPIDURAL INFUSION OF FENTANYL WITH BUPIVACAINE TO FENTANYL ALONE FOR POST THORACOTOMY PAIN RELIEF

Anaesthesiology

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ABSTRACT

Background: Optimum pain relief following thoracotomy is essential for patient comfort and to reduce the incidence of postoperative pulmonary complications.

Methods: A randomized clinical trial was conducted Amrita institute of Medical Science, Kochi. 60 patients scheduled for thoracotomy procedure in between 2009 to 2012. The patients were randomly divided into two groups. Group A received 0.125% bupivicaine with fentanyl 10 µg.ml-[1], Group B received only fentanyl 10µg.ml-[1] in a calculated dose as a continuous thoracic epidural infusion.
Adequacy of analgesia was assessed at rest and during movement over 24 hours. Analgesic efficacy was assessed using a visual analogue score and an observer verbal ranking scale.

Results: It was observed that Group A patients had lower pain score than Group B.There was no significant differences in the incidence of adverse effects among the two groups. However the use of intraoperative vasopressors was significantly higher ($p<0.05$) in Group A as compared to group B. The incidence of Nausea, Vomiting, pruritus, respiratory depression & sedation were more frequrent in Group B. No neurological complications were encountered in any of the study groups.

Conclusion: we conclude that the benefit from the addition of 0.125% bupivacaine to fentanyl (l0mcg.ml-[1]) in thoracic epidural analgesia is confined to the early postoperative period after thoracotomy.

KEYWORDS

Thoracotomy, Anesthesia

Introduction:
Pain is the "unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage".

Optimum pain relief after thoracotomy is essential, to reduce the incidence of atelectasis and postoperative pneumonia. Patients must not only be pain free at rest but must also be able to breathe deeply, cough effectively and comply with postoperative physiotherapy.

Bupivacaine, at high concentrations in thoracic epidural can produce excellent analgesia. but the incidence of hypotension with 0.5%bupivicaine is high. Epidural opioids have also been used after thoracotomy. Lipophilic drugs such as fentanyl are popular in this respect and have a lower incidence of side effects than hydrophilic opioids such as morphine. The optimum concentration of fentanyl that balances efficacy against side effects is thought to be 10µg.ml-. There has been much recent interest in attempts to improve the quality of epidural opioid analgesia by addition of low concentration of local anesthetics, with the hope of reducing the incidence of side effects.

This prospective randomized study was designed to compare the efficacy and safety of continuous thoracic epidural infusion of fentanyl (10µg.m-[1]) alone and also in combination with low concentrations of bupivacaine (0.125%) for the management of post thoracotomy pain.

Methods:
After obtaining ethics committee approval and written informed consent from the patients, study was conducted. Sixty adult patients of American Society of Anesthesiologists physical status (ASA) I , II & III between 16 to 85 years undergone elective pulmonary resection.

Patients who had pre- existing motor or sensory deficits were excluded from the study. Group A received 0.125% bupivicaine with fentanyl 10µg.ml-[1] and Group B received only fentanyl 10µg.ml-[1]

All the patient after fasting for 6-8 hrs prior to surgery were premedicated with Tab Ranitidine 150 mg, Tab Metochlopramide 10mg & Tab Alprazolam 0.25mg at previous night & 2hr before operation in morning with sips of water. On table a large bore intravenous canula was put under local anesthesia. Patient was monitored with ECG, Oxygen saturation, Temperature, end tidal carbon dioxide, Invasive monitoring of blood pressure, and central venous pressure and a mid thoracic (T4-5,T5-6) epidural catheter were inserted under local anesthesia. Test dose (2% lignocaine with 1:200,000 adrenaline) 3ml was given. Group-A received an epidural infusion 0.125% bupivacaine plus fentanyl10 µg/ml (0.1ml/kg/hr) & Group B received only fentanyl 10 µg/ml /ml (0.1ml/kg/hr) in a calculated does as a continuous thoracic epidural infusion. After pre-oxygenation, general anesthesia was induced with fentanyl 2-3 µg.ml-, Propofol 2-3 mg/kg in. neuromuscular block was achieved with vecuronium o.1 mg/kg followed by an intubation with adequate size double lumen endotracheal tube. Anesthesia was maintained with isoflurane in oxygen and nitrous oxide along with divided doses of vecuronium. A central line was placed under strict aseptic precautions through the internal jugular vein after induction of anesthesia and before positioning the patient.

Intraoperative analgesia was provided by a 0.1ml/kg bolus of epidural solution delivered before surgical incision followed by an infusion of 0.1ml/kg/hr. the infusion rate was then adjusted as per the clinical response to between 0.1 to 0.2 ml/kg/hr. Arterial pressure transducers were zeroed at the mid vertebral line.

Elevated arterial pressure was first treated by increasing the epidural infusion rate to a maximum of 0.2 ml/kg/hr. If necessary the inspired concentration of isoflurane was also increased. During surgery intravenous ephedrine was used for arterial pressure control and the total dose used was recorded.

After the surgery the patients were managed in an intensive care unit for 24 hours. Analgesia was assessed at 2, 4, 8, 16 and 24 hours using a visual analogue scale (VAS; 0mm = no pain and 100mm = worst pain (unimaginable) both at rest and during coughing. At the same time, pain was assessed using a four-point observer verbal ranking scale for pain (OVRS) described in table-1.

Table 1

Pain score	Pain experience
1	No pain : pain not restricting any activity, cough, turning onto side.
2	Mild pain : able to take maximal deep breath but movement & coughing slightly restricted by pain. physiotherapy effected.
2	Moderate pain : needs help to move onto side ;cough and deep breathing restricted by pain. physiotherapy ineffective.
3	Severe pain : pain making turning onto side impossible and/or ineffective; or patient refuses to try.

If the patient was in pain a 5ml bolus of the same infused drug was given and the infusion rate increased by 1ml.h-[1] as long as the total infusion rate remained less than 0.2ml.kg-[1]h-[1]. If this was not sufficient after 20 minutes a further 5ml bolus of the drug was given; and if after a further 30 minutes the patient was still in pain, the patient was removed from the study and intravenous narcotics or NSAID's were instituted. Any episodes of nausea and vomiting, itching, motor block or altered sensation were recorded at the same time as pain scores. The rate of infusion of epidural solution was reduced by 1ml.h-[1] if the patient was troubled by side effects as long as there was no significant pain.

Pulse rate and arterial pressure measurements were continuously recorded peri operatively to allow subsequent analysis of all episodes of hypotension. Peri operative fluid management was administered with an aim to maintain a central venous pressure (CVP) in the range of 8-10 cm of water. The blood loss was estimated and replaced with whole blood or colloid. If the SBP decreased to less than 90 mmHg, 250ml of colloid was given and the epidural rate was reduced by 1ml.h-[1]. If the SBP reading decreased to less than 80 mmHg, the epidural infusion was switched off and the patient was given up to 500 ml of colloid and 3mg boluses of ephedrine as necessary. Any interventions for hypotension were documented. Respiratory rate was recorded hourly.

If at any time the patient was found to be difficult to rouse or the respiratory rate decreased to less than 9 breaths.min-[1], the epidural infusion was switched off and the patient was re-assessed. The epidural infusion was restarted only if the respiratory rate was greater than 9 breaths.min-[1] and the patient easily roused to command. In this instance, the epidural infusion was restarted at 2ml.h-[1] lower than the previous rate.

After collection of data, it was analysed statistically. The comparison of demographic characteristics (age, height, weight, ASA), pain score & hemodynamics between two groups were done by applying independent sample student 't' test.

To test the statistical difference in the percentages of the side effects between two groups, chi square test was applied. p value of < 0.05 was considered significant.

Results:

Sixty patients were recruited for the study. Thirty patients were randomly allocated to each group. The demographic data of these patients are detailed in table 2 & 4. There were no statistically significant differences in age, sex, or weight distribution between the patients in each group.

There were no between group differences in OVRS pain scores at any time. The mean pain scores assessed by VAS at rest and with cough at different measurement times are presented in table 3. VAS pain scores while coughing were significantly higher in Group B than Group A ('p'<0.05) or at 2nd & 4th hours. There were slightly higher pain scores in Group B at other times of assessment.

The mean value for epidural solution infused in Groups A was 155ml and Group B was 149 ml (NS). Three patients in Group B and seven patients in Group A received intervention for hypotension (NS). The mean dose of perioperative ephedrine used in Groups A and B were 20 and 9 mg. Patients in the bupivacaine groups (GroupA) received significantly more ephedrine ('p'< 0.01) than those in Group B.

Table 2: Demographic data

Group	A	B
No. of Patients:	30	30
Age in years:	44±6	44±5
Weight in Kg's	62±5	64±4
Sex (Male: Female):	22:9	22:8

No: Number, Kg : kilogram

Table 3: Vas Pain scores

GR	AR	AM	BR	BM
2H	22	29	32	48
4H	20	26	30	42
8H	15	22	24	35
16H	12	16	18	27
24H	8	15	14	24

VAS: Visual analogue scale (0mm= no pain; 100mm=worst pain imaginable)

GR : Group, AR : Group A at Rest, AM: Group A at Movement, BR: Group B at Rest, BM: Group B at Movement

Six patients in Group A and nine patients Group B reported nausea (NS). Seven patients in Group A & nine patients in Group B reported pruritis (NS). No patients from Group A and B reported any motor or sensory abnormalities during the study time. Incidence of drowsiness seen more in the fentanyl group ;group B than Group A. None of the patients were sedated to a degree that made them difficult to arouse.

One patients had episodes of respiratory depression (respiratory rate of less than 9 breaths.min-1) in Group B and required the discontinuation of the epidural infusion for three hours

Table 4: Side effect observed in the study

Side effect	Group A(30)	Group B(30)
Hypotension	7	3
Nausea / vomiting	6	9
Pruritus	7	9
Respiratory depression	-	1
Sensory/ motor abnormality	-	-

Discussion

The two most common groups of pharmacological agents used for epidural analgesia are local anesthetics and opioids. Epidural bupivacaine 0.5% with the epidural catheter placed in the thoracic region results in effective analgesia after thoracotomy but is associated with an unacceptable incidence of hypotension[3]. When bupivacaine is used as the sole epidural agent in lower concentrations to avoid sympathetic blockade, analgesia is usually inadequate. Opioids have also been given by the epidural route as the sole analgesic after thoracotomy and have been shown to reduce the incidence of complications such as atelectasis and pneumonia[1,2]. Fentanyl has emerged as the suitable opioid for infusion into the epidural space at an optimal concentration of 10mcg.ml. Side effects are not frequent, but the problem of delayed respiratory depression could be encountered.

Evidence exists from animal studies that combinations of opioids and local anesthetics may have a synergistic effect when given neuraxially, The severe pain caused by thoracic surgery leads to shallow breathing, impaired ability to cough and changes in respiratory mechanics. It is therefore important to provide the most consistently effective analgesia possible for patients undergoing thoracotomy with a minimum number of side effects. For this reason we studied the analgesic effects of fentanyl at an optimum concentration when used alone and when supplemented by two low concentrations of, bupivacaine.

Our data demonstrates that the addition of low dose bupivacaine to fentanyl 10µg.ml-[1] significantly improves analgesia in the early postoperative period only. There are a number of possible explanations for this finding. Pain after surgical incision is likely to be greatest at the time of incision and then to decrease with time. In addition during an epidural infusion with fentanyl, serum concentrations of fentanyl increase steadily with time. In a study comparing lumbar epidural infusions of fentanyl with intravenous infusions of fentanyl for post thoracotomy pain, VAS pain score decreased steadily in both groups over a period of 12 hours before steady low pain scores were recorded. Simultaneously, serum concentrations of fentanyl in both groups increased steadily over a period of 12 hours before a steady state was achieved. It is controversial; whether the action of epidural fentanyl is due to a systemic effect or due to a direct spinal effect[5]. However, whichever mechanism is active in the early postoperative period, alone or in combination, our findings suggest that it is inadequate. In this situation, any benefit from the addition of bupivacaine is more likely to be evident. As concentrations of fentanyl increase, and pain stimuli decrease, the additive effects from the local anesthetic becomes less significant.

Mourisse et al, in a much smaller comparison of epidural sufentanyl with bupivacaine / sufentanyl combination, found a similar pattern with the additive effects of local anesthetic evident for the first 14 hours after surgery. The total fentanyl dose delivered was not altered by the addition of bupivacaine as there were no between group differences in

the total volume of solution infused. This has been found in previous studies and concurs with the finding that apart from the early postoperative period, bupivacaine does not improve fentanyl analgesia. Any differences in infusion rates caused by higher pain scores at 2 hours were balanced out over the first 24 hours and were not sufficient to effect differences in the total volumes of epidural infusion used.

Assessment of pain relief not only at rest, but also on moving and coughing is an essential component of studies analyzing pain relief methods.We therefore performed VAS scoring at rest and on coughing and incorporated ability to move and to cough as a major aspect of the OVRS scoring system. Fewer than 10% of studies of postoperative pain relief have examined this aspect. In addition to our larger study group we have also attempted to improve the sensitivity of the study by using more pain scoring methods.

Previous studies have also incorporated a wide variety of operations within the same treatment group. It is likely that the intensity and duration of pain after thoracotomy differs from that experienced after major abdominal surgery. Consequently, the results from such studies may differ when compared to the homogenous surgical population of our study.

There have, however been previous studies confined to post thoracotomy pain. Logas et al, with a study population of 53 patients in 5 different study groups found no benefit when epidural morphine (0.1 mg.ml-1) was compared with a combination of morphine and bupivacaine (0.1%). However, they did not report pain scores as early as 2 hours after surgery and the assessment of pain on coughing was not included. Similarly, Burgess et al reported no difference in pain scores when fentany 10µg.ml-1 was supplemented by 0.03%, 0.06% and 0.125% bupivacaine. The concentration of fentanyl used by these investigators was lower than that used in our study and should have allowed any benefit of supplemental local anesthetic to become obvious.

It was interesting to note that the VAS scores in our study appear relatively high for each time interval. However, the clinical impression was that, with the exception of the 2 hour measurement time for Group B, the overall quality of analgesia was excellent.

The use of solutions containing bupivacaine was associated with an increased number of side effects related to epidural local anesthetic. Interestingly there were no significant between group differences in the incidence of postoperative hypotension. The relative haemodynamic stability when using small concentrations of local anesthetics has been confirmed by other studies. There was however a greater need for vasopressor in the bupivacaine group (Group A > GroupB). It is likely that the sympathetic blockade effect of bupivacaine would be emphasized by the initial 0.1ml.kg-1 bolus dose and the presence of anesthetic agents. The incidence of side effects of nausea and pruritis was not significantly different between the groups and were generally mild and easily treated.

The overall incidence of respiratory depression as defined in our study was 3.3%. Leith et al documented that when epidural diamorphine was used for postoperative analgesia the incidence of significant respiratory depression was 2.6%. The dose of fentanyl used in our study and the concentration recommended when used as a sole agent[4] is relatively large. The resulting quality of analgesia appears to be at the risk of a significant incidence of respiratory depression.

Conclusion:

we have shown that the benefit from the addition of 0.125% bupivacaine to fentanyl (l0µg.ml-[1]) in thoracic epidural analgesia is confined to the early postoperative period after thoracotomy.

We therefore recommend that when fentanyl l0µg.ml-[1] is used as an infusion into the thoracic epidural space for patients undergoing thoracotomy, bupivacaine 0.125% should be added for early postoperative period only. Thereafter fentanyl alone is adequate. The incidence of respiratory depression with a concentration of fentanyl l0µg ml-[1] appears to be relatively high. So reducing the concentration of fentanyl by using 0.125% bupivacaine, the incidence of respiratory depression may be reduced without compromising the analgesic effect.

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